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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/531,648	04/15/2005	Gerard Coudert	SERVIER 453 PCT	1540

25666 7590 05/23/2007

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EXAMINER	
HABTE, KAHSAY	
ART UNIT	**PAPER NUMBER**
1624	

MAIL DATE	DELIVERY MODE
05/23/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/531,648	COUDERT ET AL.	
	Examiner	Art Unit	
	/Kahsay T. Habte/	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 May 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *14-28* is/are pending in the application.

4a) Of the above claim(s) *26-28* is/are withdrawn from consideration.

5)☒ Claim(s) *14-23* is/are allowed.

6)☒ Claim(s) *24* is/are rejected.

7)☒ Claim(s) *25* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action ~~or form PTO-152~~.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *4/15/2007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 14-28 are pending in this application.

Election/Restriction

2. Applicant's election with traverse of Group I, Claims 14-25 filed 5/7/2007 is acknowledged. The traversal is on the ground(s) that "Group II are useful as intermediates in the synthesis of the compounds of the compounds of Restriction Group I, and that these intermediates have the same structural core (i.e. the tetracyclic 1,4-oxaine core as defined by the Office) as the compounds of restriction Group I". The examiner disagrees with applicant's argument. Groups I-II don't have the same structural core structure. The core structures are different one from the other. Group I is drawn to benzo[a]pyrrolo[3,4-c]phenoxazines or benzo[e]pyrido[1,4]-oxazino[3,2-g]isoindoles that is not present in Group II. The pyrrole ring is missing from the core structure of Group II. In regard to the argument that Group II is drawn to intermediate compounds to make compounds of Group I, the examiner disagrees. Unless the compounds of Group II are transformed into other intermediate compounds, Group II would not make compounds of Group I in just one step. One skilled in the art would not consider Group II as an intermediate compound to make compounds of Group II, because the two esters (i.e. COOMe) attached to the tetracyclic ring would not form a pyrrolo ring. Groups I-II do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: the special technical feature of Group I is

benzo[a]pyrrolo[3,4-c]phenoxazines or benzo[e]pyrido[1,4]-oxazino[3,2-g]isoindoles rings (pentacyclic) that is not present in the special technical feature of Group II. The special technical feature of Group II is a tetracyclo 1,4-oxazine ring and is different from the special technical feature of Group II. In addition, the search for the invention of Group II would include search in the subclass 544/99, search in the EAST database and also search of the compounds in CAS (Chemical Abstract Services). Therefore, coexamination of each of these additional inventions would require a serious additional burden of search.

The requirement is still deemed proper and is therefore made FINAL.

3. Claims 26-28 are withdrawn as being drawn to non-elected invention. It is recommended that applicants delete these claims in response to this Office Action.

Information Disclosure Statement

4. The information disclosure statement filed 4/15/2005 fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each cited foreign patent document; each non-patent literature publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. It has been placed in the application file, but the information referred to therein has not been considered.

Note that the two International Search Reports have been acknowledged, but the EP0841337 reference and the two NPL reference (Noburu MOTOHASHI and Morgan et

al.) are missing. The dates of the International Search report are also unclear if they correspond to the date of mailing or the date of actual completion of the search report or something else. Clarification of the dates on the International Search Report and submission of the missing three references is required.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 24 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. It has been recited in claim 24 a method of treating cancer in general, but the specification is not enabled for such a scope.

A number of factors are relevant to whether undue experimentation would be required to practice the claimed invention, including "(1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the

art, and (8) the breadth of the claims." In re Wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988).

(1). Breadth of Claims: Claim 24 is are directed to a method for treating a living animal body, including a human, afflicted with cancer that comprises the step of administering to the living animal body an mount of a compound of claim 14.

Scope of use - The scope of use that applicants intend to claim is very broad. To this day, it is impossible to treat all cancers with a single pharmaceutical drug. Please see below for the explanations that cancer cells are broad and different one from the other. Cancer cells can exist in different parts of the body and the nature of these cancer cells differs one from the other. For example, the treatment of bone cancer cannot be the same as the treatment of skin cancer. The drug that inhibits bone cancer cells may require more doses than the cancer cells in skin. The form of delivery for both said cancers (radiation, ointment, tablets, etc.) is not the same. For instance, one has to get deep to the bones to inhibit the cancer cells in the bones, while applying the drug on the surface of the skin can inhibit cancer cells on skin. It is also a fact that some cancer cells need more drugs than the others. It is also true that the compounds could be having antagonistic effect or agonistic effect when administered to the body. Which diseases (cancer cells) are inhibited by the administration of the drug and which are not? Applicants claim that all cancer cells can be treated by single pharmaceutical drugs, thus is not enabled.

It can be shown that cancer cells in general are extraordinarily broad. For a compound or genus to be effective against cancer cells generally is contrary to medical science. Cancer is a disease, which can take place in virtually any part of the body. There is a vast range of forms that it can take, causes for the problem, and biochemical pathways that mediate cancer. There is no common mechanism by which all, or even most, cancers arise. Accordingly, treatments for a cancer or inhibition of cancer cells are normally tailored to the particular type of cancer cells present, as there is no, and there can be no "magic bullet" against cancer cells generally.

Even the most broadly effective antitumor agents are only effective against a small fraction of the vast number of different cancers known. This is true in part because cancers arise from a wide variety of sources, such as viruses (e.g. EBV, HHV-8, and HTLV-1), exposure to chemicals such as tobacco tars, genetic disorders, ionizing radiation, and a wide variety of failures of the body's cell growth regulatory mechanisms. Different types of cancers affect different organs and have different methods of growth and harm to the body, and different vulnerabilities.

Leukemia is a disease that affects blood forming cells in the body. It is cancerous condition characterized by an abundance of abnormal white blood cells in the body. Leukemia begins in the bone marrow and spreads to other parts of the body. Both children and adults can develop leukemia and at this time there is no real means

of prevention or successful treatment for the disease. Causes of leukemia are unknown, but researchers believe that smoking accounts for 20% of a type of leukemia that affects adults called adult acute myelocytic leukemia (AML). Radiation exposure is another factor of leukemia development.

Leukemia can be divided in to 4 types. It is first classified as acute or chronic.

Chronic Leukemias

In chronic leukemia, the leukemia cells come from mature, abnormal cells. The cells thrive for too long and accumulate.The cells grow slowly.

Acute Leukemias

Acute leukemia,on the other hand, develop from early cells, called "blasts". Blasts are young cells, that divide frequently. In acute leukemia cells, they don't stop dividing like their normal counterparts do.

Myelogenous Leukemia

Myelogenous leukemia develops from myeloid cells.

Lymphocytic Leukemia

Lymphocytic leukemia develops from cells called lymphoblasts or lymphocytes in the blood marrow. The disease can be acute or chronic, referred as chronic lymphocytic leukemia (CLL), or acute lymphocytic

This shows that leukemia is very broad and differ one from the other. Note that the nature and origin of leukemia also is different one from the other.

b. Scope of Compounds - The scope of the compounds is also broad. It is apparent that hundreds of millions of combinations of compounds can be created from the definitions, owing especially to broad scope of W_1, Z, R_1, R_2, R_3, R_4 and n.

(2). Direction of Guidance: The amount of direction or guidance is minimal. There is no guidance in the specification for the treatment of cancer in general. It is also noted that generic dosage is disclosed, regardless of the nature of the cancer cells.

(3). State of Prior Art: There is no evidence of record that compounds structurally similar to these fused 1,4-benzoxazine compounds are in use for the treatment of cancer in general.

(4). Working Examples: The working examples are limited only to just one compound (Example 2). The compound tested for cytotoxicity on cell lines (L1210, KB-3-1, DU145, A549 and HT-29). It is concluded that compound of Example 2 has an IC_{50} of 0.27μM with respect to DU145 prostate carcinoma, 0.16μM with respect to A549 non-small-cell lung carcinoma, 0.6μM with respect to HT-29 colon carcinoma and 0.26μM with respect to KB-3-1 epidermoid carcinoma, however, there is nothing in the

disclosure regarding how this *in vitro* data correlates to the treatment of cancer in general recited in claim 24. It is unclear if other compounds pass or fail the test.

(5). Nature of the Invention and Predictability: The invention is directed to treating cancer in general. It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved," and physiological activity is generally considered to be an unpredictable factor. See In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). Cancers are especially unpredictable due to their complex nature. Please refer to the earlier rejection in item 2 that shows different types of cancers. The treatment of one type of cancer could not be necessarily the same for the other type.

(6). The Quantity of Experimentation Necessary: Immense, because so many cancerous cells are covered; see part (1). Note that only one compound was tested, thus, it requires undue experimentation to test all the compounds embraced by claim 14. There is no reasonable basis for assuming that the myriad of compounds embraced by the claims will all share the same physiological properties since they are so structurally dissimilar as to be chemically non-equivalent and there is no basis in the prior art for assuming the same. Note *In re Surrey*, 151 USPQ 724 regarding sufficiency of disclosure for a Markush group.

(7). The Relative Skill of Those in the Art: The relative skill is extremely very low. To this day, there is no magic bullet that can treat cancer cells in general.

When the best efforts have failed to achieve a goal, it is reasonable for the PTO to require evidence that such a goal has been accomplished, *In re Ferens*, 163 USPQ 609. The failure of skilled scientists to achieve a goal is substantial evidence that achieving such a goal is beyond the skill of practitioners in that art, *Genentech vs Novo Nordisk*, 42 USPQ2nd 1001, 1006.

It is recommended that applicants delete "cancer" and limit the treatment to prostate carcinoma, non-small-cell lung carcinoma, colon carcinoma and epidermoid carcinoma to overcome this rejection.

Claim Objections

6. Claim 25 is objected to because of the following informalities: the recitation of "useful in treating cancer" in a composition claim has no patentable weight. It is recommended that applicants delete this phrase.

Allowable Subject Matter

7. Claims 14-23 are allowed.

Oath/Declaration

8. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because: the foreign filing date of the Foreign Application FRANCE 02/12964 in the oath shown as **10/12/2002**, but the foreign filing date in the Foreign Application FRANCE 02/12964 is shown as **10/18/2002**.

Conclusion

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kahsay Habte, Ph. D. whose telephone number is (571) 272-0667. The examiner can normally be reached on M-F (9.00AM- 5:30PM).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson can be reached at (571) 272-0661. The fax phone number for the organization where this application or proceeding is assigned is (571)-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should

you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Kahsay Habte
Primary Examiner
Art Unit 1624

KH
May 22, 2007